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ABSTRACT

This literature review, from 1990 to the present, discusses the characteristics of autism and the comorbidity of mental retardation and autism. Specific medical syndromes that complement the heterogeneity concept are described, including epilepsy, fragile X syndrome, Rett syndrome, tuberous sclerosis, and Asperger syndrome. The paper presents some genetic and medical factors in the diagnosis of autism and delineates research prospects and priorities. Results of the review indicate that autism remains a complex syndrome that seems to be more clearly defined in parameters of neurobiological and neurobehavioral and psychological descriptors. The research substantiates the organic and genetic indices of autism, but finds that the differential diagnosis is still not simple and presentation of symptoms may overlap with other atypical syndromes. Co-morbidity with mental retardation and autism is found to occur in as many as 75 percent of the cases. The construct of a continuum, compendium, or spectrum of disorders is discussed, with consideration for subgroups to explain the types of autism presented in research and clinical findings. The contributions of research in the fields of neurobiology and neuropsychology, and the technical advancement in genetic research and neuroimaging are addressed. (Contains 73 references.) (CR)

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GENETIC AND MEDICAL CONSIDERATIONS OF AUTISM: A LITERATURE REVIEW

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COLLEGE OF EDUCATION AND HUMAN ECOLOGY

BY

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DENTON, TEXAS

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Abstract

Autism remains a complex syndrome and a challenge for diagnosis despite the relative consistency in identifying characteristics since first defined by Kanner in 1943. The triad of social interaction impairment, communication deficits, and restriction of activities and interests remain basic symptoms of autism. In addition, the comorbidity of mental retardation and autism may occur in as many as 75% of cases. Many medically defined syndromes associated with autism, since autistic or autistic-like symptoms are included in diagnoses. Although autism presents as a behavioral and psychological construct, autism is now accepted as a basic biological etiology. This review focuses on mental retardation, as well as genetic and medical findings and recommendations for future research. The sciences of neurobiology, and neuropsychology, and the technical advancements in genetic research and neuroimaging are in their infancy in finding more precise answers. The convergence of these disciplines in autistic research is recognized as a positive direction and discussed in the review.

Genetic and Medical Considerations of Autism:

A Literature Review

Autism is a complex syndrome with significant behaviors and yet, undetermined etiology that is in continued stages of research. Autism is defined in the American Psychological DSM-IV and in the World Health Origination's ICD in psychological terms and associated with cognitive deficits (Rutter & Schopler, 1992). Moreover, the first description of autism by Kanner (1943) remains basically consistent with observations and descriptions since that time. The questions posed by Kanner (1971) in his follow-up analysis suggest a biochemical explanation and the need for multidisciplinary collaboration to unlock the unknowns of the syndrome. Meyers (1989) observed that diagnosis is difficult when behavioral and mental retardation are copresenting symptoms. In fact, mental retardation is associated in more than half of diagnosed autism (Bailey, Phillips, & Rutter, 1996).

Recent research and sophisticated medical technology have identified a biological etiology with neurological impairments. Gillberg (1990a) indicated that although the research and etiology of the 1980's can only be more precise in a small percentage of cases, "autism boundaries seem looser than a decade ago" (p. 113) as research continues. Neurobiological investigations are strongly recommended when autism behavioral characteristics are presented (Folstein & Pevin, 1991; & Gillberg, 1990a). The heterogeneity of the disorder is indicated as well by Tuchman, Rabin, & Shinnar, (1991b) and the importance of genetic factors and cognitive deficits are most recently reemphasized in a major review of the diagnosis of autism (Bailey, et al.1996). As a result of recent research, the interdisciplinary efforts among neuropsychological, neurobiologists and geneticists and clinicians are strongly encouraged by

those whose work spans years (Rutter, 1996) . In fact, Bailey, et al. observed that the research over the last three decades is the most extensive for a child psychiatric disorder.

The purpose of this literature review is to (a) discuss the comorbidity of autism and mental retardation (b) highlight specific medical syndromes that complement the heterogeneity concept and including epilepsy, fragile X, Rett syndrome, and tuberous sclerosis (c) present some genetic and medical factors orientation in the diagnosis of autism and (d) delineate some research prospects and priorities. The literature reviewed will focus on the years 1990 to the present although some articles of significant import prior to this period will be included. Research priorities are discussed since many authors (Gillberg, Ehlers, Schaumann, Jackobbson, Dahlgren, Lindblom, Bagenholm, Tjuus, & Blidner, 1990; Herault, Petit, Martineau, Cherpi, Perrot, Sauvage, Barthelemy, Much, & Lelord, 1994; & Rutter, 1996) identified future prospects as major issues in their writings.

Autism, Mental Retardation, and Subgroups

Classic autism was first described by Kanner in 1943 (Kanner & Lesser, 1958) . He noted specific behaviors that included the inability to relate to people in ordinary ways from the beginning of one's life; excellent rote memory skills, poor language that presented as mutant to lack of communication intent, echolia, pronoun reversal, and literalness. Kanner also noted fear of loud noises and moving objects, repetitiousness and preference for ritual and sameness in the physical environment and routine, lack of spontaneous activity and good cognitive potential. Kanner and Lesser (1958) observed that " a moderate or severe mental retardation poses more of

a problem in a differential diagnosis, especially when the children exhibit behavioral oddities..." (p. 669). The factor of mental retardation is a significant component in the differential diagnosis of autism.

Many of the characteristics identified by Kanner are defined or used in DSM-IV descriptors. Those features include involvement in life long conditions and early onset, usually recognized before three years of age. A triad of characteristics (a) social interaction impairment, (b) communication deficits, and (c) restriction of activities and interests remains constant in the literature as common features of autism (Edwards & Bristol, 1991; & Gillberg et al., 1990a).

Autism and mental retardation

A strong association between autism and mental retardation is discussed in the literature. Although mental retardation and autism need not co-present, Hooper, Boyd, Hynd and Rubin (1993) indicated as much as 70% co-diagnosis of autism with mental retardation and Bailey, et al. (1996) suggested a 75 % mental retardation association. Mental retardation is indeed a force in the diagnosis of autism. (Bailey et al.; Eaves, L. C., Ho, & Eaves, D. M., 1994; Edwards & Bristol, 1991; Gillberg et. al., 1990; Hooper, et al., Myers, 1989; & Smalley, 1990). Eaves, et al. studied a "natural grouping of children" (p. 8) with mental retardation in a study of 166 children and concluded that, in part, the "degree of autism is related to the degree of mental handicap" (p. 17). Edward and Bristol (a) reported that autism is not rare among severe developmental disabilities and disclaim the myth that "all children have potentially normal intelligence" (p. 1757) and (b) concluded that autism can coexist with mental retardation and the prevalence is three times more frequent in males than females.

Myers (1989) presented an interesting perspective on the difficulty in diagnosis of mental retardation and infantile autism. He observed that the unevenness in intellectual abilities and overall global intellectual impairment may occur with deficits in social skills and gross motor development. These copresentations can make specific diagnosis difficult. According to Meyers common misconceptions that can lead to "erroneous diagnosis" (p. 87) may include: a negative stance and inability behavior; refusal to comply with requests; deceptive bright looks; normal physiologomy and motor development; isolated normal intellectual functioning. Moreover, adequate gross motor development and physical appearance are not indicators of intelligence; nor should emotional disturbance be confused with mental retardation.

Evaluation for autism requires caution and perception. Meyers (1989) and Gillberg, et. al. (1990a) supported IQ testing as an essential as part of the diagnostic examination and the test should be appropriate for age, verbal ability, and communication abilities. Meyers recommended the use of low level evaluation instruments to assess the child such as the Catell Developmental Scales or Bayley Infant Scale. Alertness to and interpretation of surroundings, abstract reasoning, and reading comprehension, not sight word reading should be given substantial consideration in autistic assessments.

Standard intelligence testing therefore seems a valid assessment tool with autistic children. Edwards and Bristol (1991) acknowledged the use of the WISC-III and WIPPSI and, if these instruments were not reliable or valid, the Stanford Binet Scale , Leiter International Performance Scale for lower functioning children. The Bayley Scales for Infant Development were suggested for children perceived to be functioning at less than two and a half standard

deviations from the mean. The Peadbody Picture Vocabulary Test- Revised was recommended to obtain a verbal functioning score.

Gillberg et al. (1990a) recommended the Raven, Leiter, Griffins, or WISC -III intelligence tests as well as assessment for language ability and symbolic play. Since verbal skills are higher for some autistic patients, the accurate analysis of the test data is important. Rating scales for degree, severity, detail of symptoms, and intervention plans are useful, but these scales are not a substitute for sound clinical assessment and full diagnostic evaluation. Gillberg (1990a), in a research review study, also concluded that an IQ test after five years of age is a good predictor of future outcome.

In summary, mental retardation and autism can be viable copresenting conditions. Mental retardation is reported to occur in over 50% of children and adults diagnosed with autism. Valid and appropriate intelligence tests commonly used in intelligence assessment can successfully be used with those people suspected or diagnosed with autism.

Diagnosis of autism

Autism can also be a challenge to diagnosis since other medically related presentations can compound a decision. For instance, seizure disorders are reported in the literature and occur in adolescents and adults especially with IQ's of less than 70 (Hooper, et al., 1993). Neurological abnormalities occur with decreased IQ (Gillberg et al., 1990a); low IQ's occurred with low functioning adaptive behaviors (Hooper, Boyd, & Rubin, 1993). In a study of 28 cases (Gillberg et al. 1990a) reported a 75% accuracy of diagnosis based on a neurophyschiatric examination prior to age three was confirmed by a longitudinal study several months and years later.

To clinically differential mental retardation and autism indeed remains a challenge. The scope of explanations for autistic behavior attests to the difficulty in comprehending the etiology of the syndrome. Both narrow explanations that focus on cognitive-social deficits compared to a broader conceptualization that considers both the social and non-social development are presented (Bailey, et al., 1996). For instance, the latter conceptualization addressed impairments in planning and attention-control discussed by Baron-Cohen (1991), Bishop (1993), and Happe (1994). Bailey, et al. (1996) summarized some of the current research which focused on (a)face processing and responding to and difficulty in facial clues; (b) discernment of emotional information and bodily expressions of emotions; and (c) a theory of mind hypothesis of autism that is concerned with children's understanding of "mental states of pretend play, beliefs, and desires. However, Bailey, et al. cautioned that not all autistic people demonstrated all these deficits.

In a review of the current literature, Bailey et al. (1996) discussed executive function and limitations in planning and organization in autistic individuals, especially "high level planning and control of behaviour [sic] (p. 101). Executive function is defined as critical for problem solving abilities. Dennis (In Bailey, et al.) reported a deficit "executive function" as observed in neurologic patients with frontal lobe lesions. The set or framework of executive function skills include: "the abilities to disengage from the external context, inhibit inappropriate responses; plan and generate sequences or willed actions; sustain an appropriate cognitive set for staying on-task; monitor own performance and make use of feedback; flexibility shift attentional set" (p. 101). In essence, children and adults have difficulty with planning and organization (Hughes, Russell, & Robbins, 1994, Ozonoff, Rogers, & Pennington, 1991); feedback (Prior

& Hoffman, 1990); applying new cognitive sets (Hughes, et al., 1994, Ozonoff, et al. 1991). Moreover, a theory of mind impairment is suggested for approximately 80% of children with autism (Bailey, et al.).

The "theory of mind" concept and the autistic child was raised by Baron-Cohen (1991). In this theory the individual is expected to "impute mental states to himself and others..." (p. 33). He/she is expected to understand and predict human behavior and be competent in communication. In a classic study, Baron-Cohen tested children's understanding of false belief by comparing the ability of mentally retarded, Down-syndrome, normal, and autistic children. A marked inability to detect differences was shown with the autistic group despite age and reported higher IQ. The theory of mind tests correlated with "abnormal social behaviors ...and abnormal pragmatic competence in language and suggested [sic] that this cognitve deficit may indeed underlie these behavior abnormalities" (p. 35). Although the studies can be limited by different sample groups, Baron-Cohen concluded that it appeared "that severe deficits in understanding belief, knowledge, thinking, pretense, and attention are indicated in autism. On the other hand, autistic children seemed to have comprehension of desire which was indicated in approaximately 80% of children tested; also perception seemed to be in tact. Baron-Cohen offered an explanation for discerning perception and not pretense and imagination as the difference in a mental representation rather than something perceived. Another hypothesis is that the mental states difficult for autism which are imagination, pretense and belief, share the quality of "truth suspension" (p. 47). Truth suspension is difficult for autistic individuals. Mindblindness is a term Baron-Cohen (1991) used to describe the "gulf" he "imagined [sic] must exist between our effort less access to mental states and the lack of this access for people with autism" (p. 47).

Studies by Frith, Morton, and Leslie (1991) supported these findings of Baron-Cohen (1991) and elaborated the biological factors that may provide some etiological explanation for autism and mental retardation. They proposed that the whole symptom complex of autism arose from a single cognitive deficit which is yet not identified. Without a normal "theory of mind" autistic children cannot understand beliefs, feelings, and other attitudes. Without this knowledge "social relationships will be difficult to form and maintain, and empathy will be almost impossible" (p. 436). Understanding intentions behind words and appropriate language will be difficult. Frith et al., for instance, presented a convergence of causes into a single biological model (p. 438).

However, more recently Frith and Happe (1994) sought explanations beyond the theory of mind. They suggested that "there is more to autism than the classic triad of impairment" (p. 118) of communication, social interactions, and restriction of interest and activities. The mentalizing accounts have helped explain some, but not all autistic features including many clinical impressions such as 1) restricted repertoire of interests, 2) obsessive desire for sameness 3) islets of ability 4) idiot savant abilities 5) excellent rote memory and 6) preoccupation with parts of objects (p. 119). Nor can the mental test study of Baron-Cohen (1991) explain all people with autism. Frith and Happe suggested that the reinterest in executive function deficits and a central coherence theory in autism may shed some further understanding on autism and limitations of the theory of mind hypothesis. Frith and Happe observed that "this universal feature of human information processing was disturbed in autism, and that a lack of central coherence could explain" some of the deficits such as memory for sentences, related items, echoing with repair, pattern detection, sorting faces by person, and recognizing faces right-way-

up (p. 121). Notably, a weak central coherence may explain the ability of autistic subjects to see parts over the whole.

Firth and Happe (1994) extended the theory of mind thesis and discussed this concept of "central coherence" (p. 101) which "influenced a broad range of psychological functions from linguistic and social to perceptual" (p. 101). Firth and Happe (1994) sought answers to this cognitive puzzle. They noted that in autistic people the ability to find meaning from information is weak in autistism. Autistic individuals tend to interpret the environment not in a global way, but rather the information from the environment is processed in "piece meal, rather than in context." In this sense, detail rather than a gestalt vantage, such as on that on block design tests, are perceived. More normal functioning people tend to see a gestalt. The Block Design test, for instance, on the Weschler Intelligence Test for Children is less of a problem for autistic people than for those individuals with higher functioning abilities where the gestalt predominates.

Bailey et al. (1996) explained that theory of mind tests such as those developed by Baron-Cohen (1991) may detect more verbally high autistic patients. However, executive function may be a more universal quality of autism and, therefore, may be " the better candidate for a primary deficit" (p. 102).

Language still remains a serious indicator of autism. Most specifically pragmatic impairment is primary even where semantic and syntactic aspects of language are more normal (Tager-Flusberg, 1993). Bailey, et al. (1996) suggested that further research is needed to define the type of language impairment. Included is an analysis of a relationship to theory of minds and /or executive function, as well as an explanation for pretend play and repetitive behaviors, circumscribed interests and resistance to change. Frith, et al. (1991) concluded that:

> In development, neural systems interact with information from the environment to form more complex neural systems, which have specific functions. In certain parts of the brain, these functions are cognitive functions, and the underlying neural systems are also cognitive systems. Cognitive systems might be localized or distributed in the brain. Some biological abnormalities can cause cognitive abnormalities during development. The intellectual enterprise that unites biologists and psychologists is to trace this relationship. Causal analyses are an essential part of this endeavor. Theory of mind and executive and mental function are viable investigatory directions. (p. 438).

Bailey et al. (1996) as a result of their comprehensive and detailed review of literature on autism concluded that some accountability for the strong association of mental retardation and autism is needed. They recognized the genetic and severity of symptomatology associations but this approach is difficult for narrow "social" theories. These are strongly associated with "intellectual levels and intellect is then an intrinsic part of autism" (Bailey, et al., p. 105). This interpretation is different for narrow social theories. Bailey et al. questioned why mentally retarded cannot be associated with a broad concept of autism "when low IQ is so strongly assoicated with autism as traditionally diagnosed" (p. 104). Autistic intellectual scores tend to be jagged" (Frith & Happe, p. 122) and do not necessarily show the same specific patterns. As a group the comprehension sub tests tend to be low and the block design type tasks higher. Bailey et al. also raised queries regarding intelligence and dimensions of expression in the diagnosis of autism. The patterns of intellectual performance have not been completely explained by the theories. The severity in intellectual skills is recognized, but this can be across more than one area.

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Intelligence scores and lower verbal abilities are usually reported for autistic people. In a important comparative study, (Bolton, Mcdonald, Pickles, Rios, Goode, Crowson, Bailey, & Rutter, 1994) investigated familial loading for autism and Down's syndrome in verbal and performance abilities. A large portion of subjects had verbal ability below 30 and familial loading was "comparatively stronger with verbal abilities" (p. 891). Bailey et al. (1996) reported that the severity of autism symptomatology and verbal IQ to be more substantial than non verbal. In fact, Bailey et al. (1996) indicated that verbal and nonverbal abilities may play different roles in autism. The questions posed for psychological theories include how peak test performance, splinter skills, and savant talents are related...and whether they are evidence of preserved cognitive function or signs of cognitive deficit" (Bailey, et al., p. 105).

Autism, mental retardation, and language and communication remain inseparable pieces in the effort and dialogue to unlock the etiology. Interestingly, in a study of the early detection of autism (Baron-Cohen, Allen, & Gillberg, 1992) found that 80% of the selected 18 month old toddlers were successfully diagnosed with autism. The distinguishing characteristics were "pretend play, prodeclarative pointing, joint attention, social interest, and social play " (p. 839). Consensus on some issues may be evolving.

Subgroups

Gillberg (1990b) in a review article stated that the current perception of autism is based on behavioral features with multiple etiologies and "pathogenetic mechanisms" in the central nervous system. Gillberg accepted a theory that autism is a constellation of symptoms and that differences may occur from case to case. Autism is a rare disorder and ten out of 10,000 may be affected by the syndrome. Even more children may be identified, if symptoms are

presented in a milder autistic-like forms such as Asperger's syndrome, medical conditions such as rubella empbryopathy, fragile X syndrome, and tuberous scelerosis (Gillberg, et al., 1990a).

Gillberg, et al. (1990a) presented a continuum which included severe and profound menial retardation to Kanner's (1943) classic mild to moderate mental retardation profile and Asperger's syndrome of near normal intelligence. Those children with deficits in attention, perception, and motor control comprised the uppermost level of the spectrum. Rett sydrome, tuberous sclerosis, and fragile X will be the more serious medical presentations of the syndromes.

The concept of a spectrum of disorders of communication and social interaction was considered by Edwards and Bristol (1991) who recognized a central nervous system abnormality as a possible prime etiology. However, Edwards and Bristol presented a comprehensive list of 17 disorders associated with or mistaken for autism. Some of these disorders will be addressed in more detail later in this review. Epilepsy, Rett syndrome, specific infections, as well as dermatological and duerocutaneous disorders and self-injurious behaviors are included in the differential diagnosis.

Eaves, Ho, and Eaves (1994) suggested that multidisciplinary data indicated that autism can be considered as "clinically meaningful subtypes" (p. 3). In an analysis of 166 children with autistic spectrum disorders, four distinctions were made based on behavioral and cognitive areas. Over one half of the cohort was most typically defined autistic with abnormal verbal and nonverbal communication, aloofness, deficit social skills and sensory abnormalities. Those individuals with moderate to severe mental handicap was 19%. Asperger-like higher functioning patients were more aggressive and overactive. A smaller group with

impaired social and language skills, limited interests and a family history of learning problems were also identified.

In a review of literature relevant to spectrum disorders, Szatmari (1992) emphasized the validity in returning to the pervasive developmental disorder category that is inclusive of nonautistic forms or autistic-like forms. Three types distinct from autism are identified: Asperger syndrome, and two atypical autistic subtypes distinguished by a low IQ and a high IQ. No effort to discuss etiology is presented in this review.

A focus on the differentiation of groups of autistic children is examined in a small study (Tirosh & Canby, 1993) of five children with hyperplexia. Hyperpelexia was explained as "word recognition, spelling skills, and non-word reading skills ... significantly advanced compared to their expected levels" (p. 86). All verbal IQ scores were below 70 for autistic and matched samples except two that were in the 70's. Based on family and medical histories which included neurological examination, the results suggested that children with autism and hyperplexia were part of the continuum of autism, not a specific syndrome.

A thorough composite of assessment instruments is strongly recommended for diagnosis (Gillberg, 1990a). Vision, hearing, neurological, and laboratory examinations were recommended in the assessment process, as well as psychological evaluation, intelligence testing, behavior checklists, observations, and interviews. Gillberg (1990a) recognized multiple etiologies based on pragmatic, not pure theoretical precepts as more relevant in the diagnosis. Infact, even multiple etiologies may "lead to multiple treatment" (p. 209). Essentially, treatment should involve education provisions, home-based therapeutic programs, and, where indicated, use of drugs (Gillberg, 1990b).

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Neurological Considerations

In a neurological discussion of autism, disorders such as epilepsy, PKU, Rett syndrome, and fragile X syndrome are considered. The subgroup/constellation of syndrome concept is integral in an examination of these disorders and a complete diagnostic neurological biological examination is strongly recommended by Percy, Gillberg, Hagberg and Witt-Engerstrom (1990). Behavioral indices and biological-medical considerations are examined across disciplines for more global, as well as, specific assessments. Consideration of genetic factors often overlap medical and neurological diagnosis and findings and these connections will be discussed as appropriate.

Epilepsy

Epilepsy is perhaps the most common biological disorder found in autistic patients (Bailey, et al, 1996; Gillberg, et al., 1990b; Nelson, 1991; Rapin, 1991; Volkmar & Cohen, 1986; Tsai, 1996; & Tuchman, et al., 1991b) . The disorder is found in the adolescent and older age autistic patient with mental retardation of below 70 (Gillberg, et al., 1990a), and often motor deficits (Tuchman, et al., 1991) . Moreover, findings also indicated that "there is no difference in the risk of epilepsy between autistic and nonautistic dysphasic children" (Tuchman, et al., p. 1224). Epilepsy occurred in girls with mental retardation at a higher rate, 24% compared to 11% for boys (Tuchman, et al., 1990. 1991). Nelson (1991) concluded that an organic, but not necessarily perinatal etiology may be an explanation. "Subtle brain mysfunctions" are suggested by Nelson.

Seizure disorders do not have definitive explanations. Nelson (1991) gave some

insight into the difficulty between autism and epilepsy. These disorders "are mysterious entities, their etiologies especially opaque; their co-occurrence suggests the possibility of pathogenic mechanism or neural circuitry, or both. Therefore, the complexity may stimulate hypotheses for future research" (p. 765).

Fragile X syndrome

Fragile X was discussed extensively with autism (Bailey, et al., 1996; Blacken, Seller, Patella, & Van Dyke 1991; Bregman, Lechman, & Ort, 1988; Cantu, Stone, Wing, Langee, & Williams, 1990; Carpenter, 1994; Edwards & Bristol, 1991; Ho, et al., 1991; Kerby & Dawson, 1994; Lachiewicz, Spiridigliozzi, Gullion, Ransford, & Rao, 1994; Meryash, Szymanski, & Gerald, 1982; Percy, et al., 1990; & Tsai, 1996). Percy et al observed that fragile X symptoms which include "hand biting, extreme gaze avoidance, and preservative and echolic bursts of speech, and later attention span problems" (p. 662) may manifest itself as a subgroup of autistic spectrum disorders. Edwards and Bristol noted that "fragile X syndrome is the most frequently reported in association with metabolic genetic disease identified with persons with autism" (p. 14).

Fragile X is reported to be the most common form of inherited male mental retardation (Cantu, et al., 1990; Carpenter, 1994; Kerby & Dawson, 1994; Lachiewicz, et al., 1994); and is more severe among males (Carpenter). Clinical diagnosis can be difficult because of the "nonspecific nature of the finding and the changing phenotype with age" (Carpenter). Carpenter identified fragile X, 1:1250 for males and 1:2000 for females, and noted distinctions. Males tended to have elongated faces and prominent ears which usually develop after puberty. Females may be physically more normal and display only mild physical abnormalities, but also may be

shy and have social anxiety. Other behavioral characteristics are hyperactivity, hand-flapping, hand biting, and poor eye contact.

Carpenter (1994) also explained a genetic component. In fragile X families, the chromosomal mutations are termed "permutations" and found in transmitting male patients and unaffected carrier women" (p. 685). The fragile X is an X linked dominant gene. Of those with a mutation, 80% men and 35% women are mentally impaired. Inheritance increased with successive generations. The gene is "expressed early in embryonic development and in various tissues with the highest expression in the brain and testes" (p. 685). This pattern, the "Sherman paradox" infers that "grandchildren of transmitting male patients are more likely to be affected than siblings of transmitting male patients" (p. 685). Carpenter suggested that "transmission through a woman increased the risk of an affected offspring, especially if the mother is mentally impaired" (p. 685). If a mother is mentally retarded, the likelihood of transmitting the syndrome can occur. Carpenter continued to explain that mutational expression may occur and expand the "linkage " themes. However, direct DNA analysis is replacing, but should not eliminate cytogenetic analysis, because of other chromosome anamolies. These anamolies can be detected and contribute to the knowledge of disorders including autism and mental retardation. Carpenter recommended genetic counseling when the X mutation is discovered.

Bremen et al. (1989) in a preliminary study of 14 males reported fragile X as a new X linked genetic disorder with significant mental retardation implications and behavioral disturbances. Specific facial contour, development of ears, and cognitive and language impairment are distinctive. Bremen et al. were reluctant to associate autistic-like disturbances to

an autistic disorder, anxiety disorder or a "neuropsychiatric syndrome specific to fragile X syndrome (p. 352).

Ho, et al. (1990) reported that family's with autism and other developmental disabilities may test positive to the fragile X chromosome and, therefore could develop the diverse manifestations of the disorder as well. This syndrome is a common and inheritable mental retardation form, yet may present as slow learner, learning disabled, attention deficit disorder, anxiety disorder, moderate mental retardation, or autism. The recommendation for cytogenetic study of siblings in families to increase the precision of diagnosis was recommended. Ho et al. reported a 3-8% autistic populaltion to be fragile X positive and may be a cause of autism and mental retardation.

In another study (Cantu, et al, 1990) found the fragile X chromosome to be of low prevalence among the patients with autistic behavior and mental retardation. Other reports (Kerby & Dawson, 1994) confirmed distinctive features of fragile X cases regarding a psychological profile. In this study nine males with mental retardation believed attributable to fragile X were compared to mental retardation with other etiology such as autistic, schizoid, and schizotypal features. In temperament, the fragile X men were more generally shy, socially withdrawn, less energetic, or emotional.

The overlap in identifying fragile X and autism is further investigated by Smalley (1991). Although a definitive association is still unclear, an overlap in characteristics is presented: lack of eye contact, gaze aversion, language deficits in grammar, abstraction, abnormal aphasia. Bizarre responses to environment were reported in males.

In a study of 55 boys with fragile X, Lachiewicz, et. al. (1994) sought to detect behavioral abnormalities in boys, to make a distinction between fragile X boys with autistic or pervasive developmental delays. A distinction was found in 21 items that included abnormal language, tactile defensiveness, poor self-control, poor eye contact/shyness, and hand flapping. Boys with fragile X demonstrated tactile defensiveness and abnormal language more frequently. Further research was indicated.

Rett Syndrome

Rett syndrome is referenced in the autistic literature because of its autistic-like syndromes (Bailey, et al., 1996; Edwards & Bristol, 1991; Gillberg, 1989; Olsson & Rett, 1987; Perry, 1991; Percy, et al., 1990; Rapin, 1991; Rutter & Schloper, 1992; Rutter, 1996; Schaefer, Thompson, Bodensteiner, McConnell, Kimberling, Gay, Dutton, Hutchings, & Bray 1996; & Volkmar, 1996). Rett syndrome and autism are reported to have possible brainstem "pathophysicological abnormalities" that reveal similar symptoms Gillberg, (1989). Rett syndrome is a generative disease and, in part, the onset and course of the disorder and identification of symptoms may make the diagnosis more difficult, but is important in the differential diagnosis when symptoms present similarly. Considerable overlap between Rhett syndrome and autism is reported. However, the suggestion for relationships is relevant to understanding the etiology. Diagnosis is difficult and Gillberg (1989) suggested a common "pathogenetic denominator in both clinical sundromes" (p. 558) Gillberg (1989) suggested that Rett syndrome will probably be found in about half of girls diagnosed with autism. Gillberg (1989) concluded that

> Whether autism cases with a known pathological represent phenocopies of some form of 'true autism' with a single etiology, or whether autism as a behavioral syndrome represents the final common pathway for various kinds of organic conditions that impair similar brain systems, remains an unresolved issue... It is quite possible that Rett syndrome too might represent a condition with considerable phenotypical and perhaps etiological heterogeneity (p. 558).

Olsson and Rett (1987) described the common characteristics usually associated with females as early behavioral psychological, and social regression, "loss of purposeful hand use and hand wringing" (p. 429). Also, females had normal head circumference until the size diminished at about four to six years of age. In this report a distinction is made between Rett syndrome and infantile autism. This disorder with its autistic-like symptoms, has led Percy et al. (1990) to focus on the separation of autism into "distinct nosologic entities" (p. 659). The concept of a continuum of diagnosis may be viewed then as more "administrative" in function "than symptomatic and descriptive" (p. 659). Moreover, Percy, et al. (1990) still recognized an organic basis for this syndrome.

Tuberous sclerosis

Tuberous sclerosis, a disorder characterized by numerous soft tissue tumors both inside and outside is associated with mental retardation. The association with autism is reported in the literature (Bailey, et. al, 1996; Gillberg, I. C., Gillberg, C., & Ahlsen, 1994; Smalley, 1991; & Williamson & Bolton, 1995). In a study of 32 children under three years of age,. Gillberg, et al. (1990a) reported a prevalence rate of 61% of tuberous sclerosis with autism, most presenting with clear symptoms. Epilepsy, mental retardation, and autistic like behavior under the age of

five "appears to have a strong correlation with tuberous scelerosis" (p. 54). In earlier studies (Gillberg, et al. 1992) reported as low as 17%.

Smalley (1991) discussed tuberous sclerosis as an autosomal dominant disorder involving benign growths in one or more organs. This disorder is genetically associated with autism. Behaviors that are autistic-like or psychopathological were identified in this study among autisic and tuberous sclerosis individuals. Smalley presented considerations for diagnosis: a medical diagnosis precluding behavioral diagnosis and variations in presentation of the syndrome. Sclerosis is also identified with autism. Gillberg et al. (1994) recommended that tuberous sclerosis "always be considered in the examination of aetiological [sic] factors" (p. 55)

Asperger syndrome

Asperger syndrome is recognized as a high order functioning syndrome compared to many other disorders and is considered often in the context of a spectrum of disorders. Historically an association with autism is reported in the literature (Bailey, et al., 1996; Bowman, 1988; Ghaziuddin, M., Tsai, Ghaziuddin, N., 1992; Rickarby, Carruthers, & Mitchell, 1991). In a review of the motor symptoms associated with Asperger syndrome, Gillberg et al. (1994) discussed the "lack of consensus about the clinical features" (p. 651). The accepted symptoms include social isolate, odd and pedantic speech, poor nonverbal communication, preoccupation with idiosyncractic interests, and clumsiness. However, since Asperger syndrome is a higher order syndrome, less focus is given to Asperger's syndrome in this review.

However, some reports are noteworthy. No conclusive data to definitively link clumsiness to autism is reported (Gillberg, et al., 1994). In a limited study of Asperger patients,

Rickaby et al. (1991) denoted "a vulnerability of a structure in the central nervous system" as a possible etiology. He did not equate maternal health or early life habits as a causality. A higher incidence of males, 10 and 20 to 1, is reported (Rickarby, et al., 1991).

Genetic Considerations

Genetic investigation for the etiology of autism is a dominant research direction (Bailey, Lecouteur, Gottesman, Bolton, Simonoff, Yuzda, & Rutter, 1995; Bailey, et al., 1996; Bowman, 1988; Blackman, Seller, Patella, & Van Dike, 1991; Bremen, et al, 1988; Holstein & Kevin, 1991; Herald, et al., 1994; Seshardri, Wallerstein, & Burack, 1992; & Smalley, 1991). Since genetic research is in its infancy, much of the studies constitute an array of data, rather than a composite or integration of information.

Folstein and Pevin (1991) described three types of genetic disorders: familiar aggregation of autism identified in sibling studies; other disorders in families that are medical, but "conceptually related to autism; and association with the disorder of known genetic etiology" (p. 767). The other conditions are cognitive deficits, personality characteristics, speech and language abnormalities, and psychiatric disorders.

Chromosomal

Genetic influences in disorders may take several approaches. Smalley (1991) reported two methods in genetic influences in autism, but recognized that although gene involvement is recognized, the exact mode of inheritance (e.g. major gene or multifactorial) is not clearly determined. One approach in behavior genetic research involved relating phenotypes to descriptors in familiar patterns and "cosegregation" or linkage evidence of a trait. The second

approach involves identification of a single gene or chromosome. A combination of both are valid as well.

In a study of a cohort of 72 each of autistic and nonautistic children, Herault, et al. (1993) reported a lack of association between genetic markers of brain growth and infantile autism. In comparison, a recent study of twins (Bailey, et al., 1995) reported a genetic basis for autistic disorders. Obstetric and environmental factors were studied, but these "hazards usually appear to be consequences of genetically influenced abnormal development, rather than aetiolgical [sic] factors" (p. 63). In this study, the genetic basis of the disorder is identified with the probability of multiple genetic loci Among factors considered were premature labor percipitated by fetal abnormalities, presentation in the birth canal, weight differences among newborns, and twins, variations in features associated with gestation periods, maternal age, and twinning. Whether twinning was the cause or consequence of autism was presented as a querie. Increased head circumference was also reported for autistic children in this study.

In another study, Spiker, et al. (1994) indicated that genetic factors play a significant role in some cases of infantile autism. Multiplex families indicated a high predisposition for autism. Thirty-seven of 44 families (87%) had at least two children who met the diagnostic criteria for autism; 71% met all autistic criteria, 22% met none of the criteria, and 7% were uncertain since some criteria was met (p. 27). Interestingly, "autistic siblings" were not concordant for most characteristics especially for IQ and verbal ability. Significant relationships were noted for behaviors related to rituals and repetitive play and response to emotions.

Smalley (1991) reported that prior to 1990 the genetic influence was supported through family and twin studies. Smalley concluded that strong familiar factors for heredity in

between 80%-90% based on multifactorial mode and sibling risks of 3% and 5%. The occurrence among monozygote (MZ twins) is reported. IQ's detecting mental retardation were in 87% of cases and 50% of IQ's were below 50. Despite the twin reports, multifactorial inheritance and environmental factors are not ruled out.

Chromosomal abnormalities are significant discoveries in answering some fundamental etiological questions. Akefeldt and Gillberg (1991) reported several case studies with specific chromosomal deletions or abnormalities. The suggestion is a possible connection between hypomelanosis and autism. A specific chromosomal link for autism is suggested by Seshadri, et al. (1992). They detected a deletion of a specific 18q chromosomal abnormality without other phenotypical features. The genetic inheritance was not fully obtained, but indications are that further study might be helpful in understanding this genetic theory for autism. In another case study, Blackman, et al. (1991) reported that the etiology for autism may be associated with "a partial duplication of the short arm chromosome Y" or what is described as isodicentric Y" (p. 162).

Bolton et al. (1994), in an important study of 99 autistic and 36 Down's syndrome probands that investigated family history, concluded that "the findings suggested that the autism phenotype extends beyond autism as traditionally diagnosed; that actiology [sic] involves several genes; that autism is genetically heterogeneous; and that obstetric abnormalities in autistic subjects may derive from abnormality in the foetus [sic]" (p. 877). Moreover, despite questions raised regarding sex differences in familial loading, more severely mentally retarded autistic types, or with speech in some autistic individuals, the genetic component remains viable. Bolton et al. concluded that

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> it has to be borne in mind that genetic heterogeneity characterizes most medical conditions with a strong genetic component and should be an expected feature of autism. It is noteworthy, in this repsect, that some of the early family studies of autism identified an elevated rate of mental retardation among siblings.... (p. 897).

Neuroimaging

Neuroimage studies (Courchesne, 1991; Courchesne, E., Press, & Courchesne, R. Y., 1993; Courchesne, Press, Yeung-Cochesnes, 1993; Couchesne, Saitoh, Yeung-Couchesne, Press, Lincoln, Haas, Schreiman, 1994; Filipek, 1996; Bauman, 1991 Holyroyd, Reiss, & Bryan, 1991; Mineshew, 1991; & Schaefer, Thompson, Bodensteiner, McConnell, Kimberling, Gay, Durron, Huchings, & Gray, 1996) present further insight into the etiology of autism.

Brain research through imaging provides additional information into the complex etiological factors although, like genetic research, neruoimaging is in early stages of development. Lack of a consistent presentation for a common site or abnormality in areas of cerebral hemisphere, thalamus, lenticular nuclei, and caudate nucleus was shown in early studies (Couchesne, 1991). Rather, the cerebellum is the only structure for evidence of abnormality, especially for cell loss when examined as autopsy. Courchesne concluded that the technology is insufficiently sensitive at this time.

Physiologic studies (Mineshew, 1991) revealed abnormalities in the cerebral cortex detected by electronencephalogrpahy. Association cortex studies used positron emissions (PET) tomography and nuclear magnetic resonance (NMR) spectroscopy. In these studies, epilepsy was found to be part of the clinical manifestation of the brain dysfunction rather than a

concurrence of separate disorders. Moreover, Minshew reported three localizations considered for autism: "dysfunction in the cortical mechanisms for selective attention ...limbic mechanisms for information acquisition...and dysfunction in informational processing by association cortex and its distributed network connections" (p. 778).

A genetic disorder, Joubert syndrome, associated with the cerebellar vermis is reported by Holyroyd et. al., (1991). This syndrome was described for a male and female with perseverance and preoccupation traits and stereotypic traits, and social interaction and communication impairments respectively. According to this study, this autistic-like behavior and developmental delay disabilities supports further indices for a possible genetic basis.

Courchesne et al. (1993) examined the brain structure of 21 healthy autistic patients. Parietal lobes were found to be abnormal in 43% of autistic patients. Cortical volume loss, white colue matter loss in pareietal lobes, and thinning of corpus callosum occurred in a portion of the autistic population. Abnormalities were bilateral. Courchesne et al. concluded, in part, that "early-onset altered development and late onset [was] progressive atrophy" (p. 387).

The identification of abnormality of cerebellar vermian lobules VI and VII in infantile autism occurred across all ages of the autistic patients in another magnetic resonance imaging study by Courchesne (1994). The two types of autistic patients were identified on the basis of presence of hypoplasia hyperplasia. Environmental or genetic origins were suggested for hypoplasia or a diminished growth in this area.

Schaefer et al. (1996) reported conflicting information to support a relationship between cerebella vermal lobule hypoplasia and autism based on quantitative magnetic resonance image

analysis. The abnormalities in lobules VI and VII are nonspecific and occurred in several conditions without autism. Also, relative cellular vermeil lobules, VI and VII hypoplasia, were found in patients with Rett syndrome and Soto's syndrome. Various processes could affect cerebella development and involve the lobules, yet not be specific for autism.

Bauman (1991) reported that the abnormalities for autism may be confined to the cerebellum and the related inferior olive. He observed that normal development of portions of the limbic system and cerebellum circuits occur. Preserved olivary neurons exist with Purkinje cell loss and some increased "cell-packing density with no reduced neuronal cell size, and an absence of gliosis" (p. 794) . The preserved olivary neurons suggested to Bauman that abnormalities occurred before birth. In both summary and prediction, Bauman observed:

> Thus, the anatomic defects in the autistic brain appear to have been acquired early in the development and are in areas that are critical to normal behavior, cognitive, and memory function. These abnormalities may well be related to the pronounced difficulties in social interaction, language function, and learning that characterize the autistic patient (p. 795).

Filipek (1996) in a review of the state of neuroimaging for the past ten years introduced caution regarding any findings. The cohorts are often heterogeneous for age, sex, IQ, and neurophysological and behavioral parameters. Controls were not uniformly matched. Moreover, variability in imaging slicing, thickness, newness, position, and orientation can yield various results. Combinations of methods of qualitative and quantitative image methods can yield heterogeneous results. Filipek suggested that future studies use larger cohorts, are limited to

presentations; (d) availability and certainty in the diagnosis of very young children who receive a diagnosis of developmental disorders; (e) repetitive patterns of behavior and unusual cognitive abilities; (f) functional associations rather than statistical correlates between autism and other medical correlates such as fragile X syndrome and tuberculous sclerosis; (g) investigation of gender association with types of autism and autistic-like conditions; and (h) conditions of epilepsy, megalocephaly and relationship to congenital condition. Studies that investigated the relationships of executive function, central coherence theories, characteristics are suggested by Bailey, et al. (1996) .

Research indeed is tackling many fronts. Rutter (1996) proposed studies that compared social impairment in autistic patients with social impairment in other pathological groups as well as detect variants in behavior in autistic patients. More refined and advanced imaging studies are still needed (Filipek, 1996) that provide more functional information (Filipek, 1996; & Rutter, 1996). Rutter (1996) also advocated for more autopsy studies. Bolton et al. (1994) recommended further "definition of the phenotype involving family study of children with autism and profound retardation" (p. 897). Gillberg (1989) contended that the area of the "nervous system connecting telencephalic, diencephalic, cerebellar, and meduallar centers, is one of the most profitable on which to focus neuropathological research" (p. 558).

In many studies the limited number of subjects in the cohorts was of concern and efforts to increase the size of samples to validate findings is strongly proposed (Rutter, 1996; Smalley et al., 1990; & Spiker et al., 1994).

Summary and Conclusion

Autism remains a complex syndrome that seems to be more clearly defined in parameters of neurobiological and neurobehavioral and psychological descriptors (Rutter, 1996). Earlier inroads in this direction are reported in a review by Gillberg (1990a). Recent research substantiated the organic and genetic indices of autism and contributed to greater consensus among practioners and researchers. However, the differential diagnosis is still not simple and presentation of symptoms may overlap with other autistic-like or atypical syndromes. The construct of a continuum, compendium, or spectrum of disorders is presented with consideration for subgroups (Smelly, et al., 1990) to explain the types of autism presented in research and clinical findings.

Diagnostic research crosses many disciplines. Prenatal, perinatal (Nelson, 1991; Peven, Simon, Chase, Wzorek, Landa, Gayle, & Folstein, 1993), radiology imaging (Courchese, 1991; Courchese E., Press, & Courchesne, R.. Y. 1991; Courchese, et al., 1992), and genetic investigations (Bailey, et al., 1995; Blackman, et al., 1991; Folstein & Pevin, 1991; & Seshardri, et al., 1992), neurological (Gilberg et al., 1990a, 1990b) continues to search for more precise diagnosis. Many theories are emerging that may provide substantive and conclusive evidence to unriddle the etiology and, even the subtle mysteries of autism.

The increase of information has paralleled developments in microbiological and technological radiology. However, the potential for increased knowledge hinges on the depth of the queries posed by researchers, the technological capabilities of research, and continued coordinated efforts and dialogue among neurobiological, neruopsychological, and radiological scientists.

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